REMARKS

Claims 1-36 remain in this application. Claims 1, 7, 8, 10, 13, 14, 15, 19, 20, 22, 25, 26, 28, 29, 31-33, and 35 are currently being amended. Support for the amendments to the claims is found in the specification and claims as filed, and at least at page 1, lines 5-6, and page 5, lines 4-5.

I. DISCLOSURE OBJECTED TO, MINOR INFORMALITIES

A. The disclosure has been objected to because of the following informalities: on page 22, line 7, in the recitation "patents". The above amendments correct this typographical error as well as another typographical error in the same paragraph at line 11, and typographical errors in the paragraphs beginning on page 5, line 18; page 10, line 8; and page 19, line 5. The Applicants believe that this objection is moot in view of the amendments to the specification, and respectfully request that it be withdrawn.

II. CLAIMS REJECTION UNDER 35 U.S.C. § 112, 2nd PARAGRAPH

Claims 1-24 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Applicants believe that this rejection is moot in view of the amendments to the claims, and respectfully request that it be withdrawn.

A. Claims 1, 7, 13, 19 and 28 are stated to be indefinite in the recitation "2-clorodeoxyadenosine", a misspelling of "2-chlorodeoxyadenosine" which is correctly spelled in other claims and in the specification. The applicants respectfully submit that such a typographical error is a matter of form, not substance, and does not make the claims indefinite under 35 U.S.C. § 112, second paragraph. These claims have been amended to correct this error. Claims 10, 20, 22 and 29 are also amended to correct any error in the spelling of 2-chlorodeoxydenosine. The rejection is moot and should be withdrawn.

B. Claims 1-12 are rejected as duplicates of claims 13-24. The Applicants respectfully submit that this rejection is moot in view of the amendments to the claims, and should be

III. CLAIMS REJECTION UNDER 35 U.S.C. § 102 (b).

A. Claims 1, 13, 25, 30-32, 35 and 36 stand rejected under 35 U.S.C. 102(b) as being anticipated by Nawrocki et al. (Transplantation Proceedings, Vol .28, No. 6, pp. 3538-35-39, 1996). Applicants believe that this rejection is unwarranted, and respectfully suggest that it should be withdrawn.

The Nawrocki et al. reference does not teach or suggest the present claimed invention, a method of ameliorating chronic allograft rejection in a human or animal allograft recipient comprising administering to the recipient in need of such treatment, in combination, a therapeutically effective amount of cyclosporin and a therapeutically effective amount of 2-chlorodeoxyadenosine. In the Nawrocki et al. study, "[c]ardiac allograft survival was determined by daily palpation, and rejection was considered complete at the time of cessation of palpable heart beat." No histology was performed; no gross pathology or histopathology of the rejected allografts were reported. The data reported are graft survival time, and while the combination therapy produced significant increases in survival time compared to untreated controls, and groups treated with either drug alone, the average survival time if the combination treatment group was only 21.28 ± 5.25 days post-transplant. No graft survived longer than 33 days. This study simply did not deal with chronic allograft rejection.

The hallmarks of chronic rejection "are persistent perivascular inflammation, often with low-level of lymphoid activation, and a concentric generalized intimal thickening of all intragraft intramural arteries to the level of arterioli. See Häyry, P., et al., "Molecular biology of chronic rejection and predictive value of biopsies," pp. 77-106 in Solez, K., et al., eds. Solid Organ Transplant Rejection. Mechanisms, Pathology and Diagnosis, Marcel Dekker, Inc., New York, 1996, at page 100 (copy provided in Supplemental Information Disclosure Statement submitted herewith). The histopathology of chronic rejection differs from that of acute rejection: acute rejection leads to the typical clinical observation of inflammation and chronic rejection leads to general, concentric arteriosclerosis in allografts. Häyry, P., 1996, Pathophysiology of chronic rejection, Transplantation Proceedings, 28 (6) Suppl. 1:7-10 (of record, copy attached for the Examiner's ready reference). Nawrocki et al. do not report data that disclose or suggest that treatment with combination amount of cyclosporin and 2-chlorodeoxyadenosine is effective for amelioration of chronic rejection. Given that Nawrocki et al. report an average graft survival in

the untreated control group of 7.13 ± 0.35 days and only 21.28 ± 5.25 days in the combination treatment group, in the absence of the diagnostic histopathology, it would be more reasonable to conclude that the Nawrocki et al. reference discloses the treatment of acute rejection, not chronic rejection.

The Nawrocki et al. reference thus neither discloses nor suggests the present claimed invention. The rejection of Claims 1, 13, 25, 30-32, 35 and 36 under 35 U.S.C. 102(b) as being anticipated by Nawrocki et al. is unwarranted, and should be withdrawn.

B. Claims 1, 3, 13, 25, 27 and 30-32 stand rejected under 35 U.S.C. 102(b) as being anticipated by Schmid et al. (Eur. Surg. Res., Vol.30, pp.61-68, 1998). Applicants believe that this rejection is unwarranted, and respectfully suggest that it should be withdrawn.

The Schmid et al. reference does not teach or suggest the present claimed invention. In the Schmid et al. study, animals were sacrificed on day 10 following transplantation, and graft histology was assessed. The histopathology reported for heart transplants was graded as mild, medium or severe using a classification system for acute heart allograft rejection. "The ISHLT classification (Billingham, M.E., et al., 1990, A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart rejection study group, J. Heart Transplant 9: 587-593) for acute heart allograft rejection classifies rejection 'mild' if focal or diffuse perivascular or interstitial infiltrates are present without evidence of myocyte necrosis, 'moderate' if the infiltration is more aggressive and focal myocyte damage is present, and 'severe' if the infiltrate consists also of polymorphs and there is evidence of edema, hemorrhage, vasculitis, and widespread myocyte necrosis." Häyry, P., et al., 1996 at page 79. The Schmid et al. reference clearly states that their report concerns the treatment of acute, not chronic, allograft rejection: "In summary, our results suggest that combining 2-CDA in a non-toxic dosage with low-dose CSA is highly effective in preventing acute rejection after allogenic heart and liver transplantation in rats." Schmid et al. at page 67.

The Schmid et al. reference thus neither discloses nor suggests the present claimed invention. The rejection of Claims 1, 3, 13, 25, 27 and 30-32 under 35 U.S.C. 102(b) as being anticipated by Schmid et al. is unwarranted, and should be withdrawn.

C. Claims 1, 3, 13, 25, 27, 28 and 31-36 stand rejected under 35 U.S.C. 102(b) as being anticipated by Cramer et al. (Transplantation Proceedings, Vol. 29, page 616,

1997). Applicants believe that this rejection is unwarranted, and respectfully suggest that it should be withdrawn. The Cramer et al. reference neither teaches nor suggests a dosage regime as disclosed and claimed in the present invention. The Cramer et al. reference discloses an amount of drug to be administered per kg, but does not teach or suggest whether that amount is to be administered once in the 90 day period, one or more times a month, one or more times a week or one or more times a day. The Cramer et al. reference thus neither discloses nor suggests the present claimed invention. The rejection of Claims 1, 3, 13, 25, 27, 28 and 31-36 under 35 U.S.C. 102(b) as being anticipated by Cramer et al. is unwarranted, and should be withdrawn.

IV. CLAIMS REJECTION UNDER 35 U.S.C. § 103 (a).

Claims 1-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nawrocki et al. (Transplantation Proceedings, Vol. 28, No. 6, pp. 3538-3539, 1996) taken with Schmid et al. (Eur. Surg. Res., Vol. 30, pp-61-68, 1998) and Cramer et al. (Transplantation Proceedings, Vol. 29, page 616, 1997). As discussed in detail above, none of the cited references, alone or in combination, teach or suggest the present claimed invention. Both the Nawrocki et al. reference and the Schmid et al. reference report short-term studies of acute, not chronic, rejection. As discussed above, the differences between acute rejection and chronic rejection are known in the art. The combination Schmid and Nawrocki with the Cramer et al. reference does not cure the defects of the Nawrocki et al. and the Schmid et al. references. The rejection of Claims 1-36 under 35 U.S.C. 103(a) as being unpatentable over Nawrocki et al. taken with Schmid et al. and Cramer et al. should be withdrawn.

CONCLUSION

In view of the amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone call would expedite the prosecution of this case, the Examiner is invited to call the undersigned at (508) 416-2433.

Respectfully submitted,

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